REMARKS/ARGUMENTS

I. Preliminary Remarks and Amendments

Claims 55-60 were pending in the application. In the present amendment, claims 59-60 have been canceled and claims 81-89 have been added. Accordingly, claims 55-58 and 81-89 will be pending in the application upon entry of the amendment. More particularly, claim 57 is amended to depend from both claims 55 and 56. Consequently, claims 59 and 60 are redundant and, therefore, are canceled herein. New claims 81-89 are drawn to aspects of the invention disclosed throughout the application, and in particular at page 2, line 18 to page 6, line 18. The amendments do not introduce new matter.

Applicants do not intend, with these or any other amendments, to abandon the subject matter of claims previously presented, and reserve the right to pursue such subject matter in duly filed continuing patent applications.

II. Patentability Arguments

A. The Rejection of Claims 55-57 and 59 under 35 U.S.C. § 103(a) May Properly Be Withdrawn.

The Examiner maintained the rejection of claims 55-57 and 59 under 35 U.S.C. § 103(a) as assertedly obvious over Busfield (US 2002/016689A1; hereinafter "Busfield") in view of Hopp et al. (Hopp et al., *Proc. Natl. Acad. Sci. USA* 78: 3824-28, 1981; hereinafter "Hopp") and in further view of Lok et al. (U.S. Patent No. 5,965,704; hereinafter "Lok") for reasons of record. Claim 59 has been canceled, thereby rendering moot the rejection of that claim. Busfield was cited for assertedly disclosing an antibody that selectively binds to an isolated fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or 12, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2 or 12 (citing Busfield at paragraphs 169-181). SEQ ID NO: 2 of Busfield is asserted as sharing 100% identity to SEQ ID NO: 2 of the instant application. The Examiner acknowledges that Busfield does not teach making an antibody specifically against the PEDPSD hexapeptide of Busfield's polypeptide comprising SEQ ID NO:2. Office Action at page 3. Hopp is cited for assertedly teaching that the best antigenicity is obtained by using hexapeptides, especially peptides rich in

amino acids P, E, and D. The Examiner contends that a person of ordinary skill in the art would have been motivated to take the teachings of Busfield under advisement, since the art was recommending hexapeptides rich in P, E, and D for excellent results. Lok was apparently cited for teaching the use of an IL-22RA (Zctyor11) polypeptide (SEQ ID NO: 2) for preparing antibodies that bind Zcytor11, which has a sequence assertedly identical to SEQ ID NO: 2 of the instant application. Office Action at pages 2-4. Applicants traverse the rejection for the reasons of record and the reasons provided below.

The Examiner's position is flawed because it selectively relies on the disclosure of Busfield and because it misconstrues and consequently misplaces reliance on Hopp, ultimately leading to the impermissible hindsight reconstruction of the claimed subject matter.

In a passage of Busfield upon which the Examiner has relied, the publication expressly recites that "[t]he antigenic peptide of a protein of the invention comprises **at least 8** (preferably 10, 15, 20, or 30) amino acid residues . . . ." Busfield, page 16, paragraph 169, lines 12-18; emphases added. The passage continues, reciting a series of antigenic peptide sequence sources, i.e., SEQ ID NOs:2 and 4-29. Importantly, Busfield characterized the antigenic peptides of the invention as being "at least" 8 amino acids in length. One cannot ignore this express disclosure and selectively rely on Busfield's asserted disclosure of the sequence of full-length IL-22RA. In specifically addressing the IL-22RA protein, Busfield established that "at least" 8 amino acids were to be found in antigenic peptides of that protein. The only way that the Examiner could have selectively relied on Busfield's disclosure of the sequence of IL-22RA while ignoring Busfield's express recitation that antigenic peptides of such a protein contain "at least" 8 amino acids is by the impermissible hindsight reconstruction of the claimed subject matter.

The Examiner combined the disclosure of Busfield with Hopp, arguing that "Hopp et al. teach that the best antigenicity is obtained by using hexapeptides (p.3826- Table 3) and especially peptides rich in P, E and D (p.3826- Table 2)." Office Action at page 3. As in prior communications, the Examiner maintains that Hopp provides a reason to use a hexapeptide from Busfield's IL-22RA as an antigenic peptide. The Examiner's position is flawed because it relies on a misunderstanding of the Hopp disclosure. Hopp does not teach or suggest the use of hexapeptides as antigenic peptides. Hopp discloses an algorithm for identifying the most likely antigenic determinant in a protein of interest. Thus, Hopp teaches the use of protein

subsequences as markers for antigenic determinants. Hopp's method involves the progressive scanning of subsequences of a protein to identify the subsequence having the highest hydrophilicity value, which will be a sequence likely within or adjacent to the sequence of an antigenic determinant in that protein. Hopp initially assigns hydrophilicity values to each of the 20 common amino acids, followed by calculations of the average hydrophilicity of each hexameric sequence of a protein scanned from one end to the other end of the primary sequence of the protein.

The hexameric sequences disclosed in Hopp are abstractions from the protein of interest and are not direct correlates of any peptides disclosed or suggested in that reference. Hopp, in fact, expressly states that "[o]nce the complete set of averaged values is obtained, the list is scanned to locate the highest value. According to the studies presented here, this high point will invariably lie **within or** be immediately **adjacent** to one of that protein's antigenic determinants." Hopp, page 3824, right column, third paragraph; emphases added. The "high point" is the highest average hydrophilicity value of a hexameric sequence found within a protein of interest. That sequence, by Hopp's own words, lies **within or adjacent** to an antigenic determinant. If the hexameric sequence lies within the antigenic determinant, the sequence of the antigenic determinant, and hence a peptide exhibiting the antigenic determinant, must be greater than 6 residues. If the antigenic determinant is adjacent to the hexameric sequence, Hopp provides no guidance regarding length/size. Consistently, Hopp recites that "[s]ynthesis of short peptides should verify that these sequences are **in**, or immediately **adjacent** to, antigenic determinants." *Id.* at page 3826, right column, fourth paragraph; emphases added.

Further establishing that Hopp did not teach or suggest the use of hexameric peptides as antigenic peptides are the statements in Hopp comparing its analytical method to a method disclosed in Rose and Roy, Proc. Natl. Acad. Sci. (USA) 77:4643-4647 (1980), which is reference 8 in Hopp. At page 3827, right column, first paragraph, Hopp states that "Rose and Roy use a least-squares fitting of data to a quadratic polynomial with a seven point moving window rather than hexapeptide averaging. This results in greater smoothing of the profile and end effects. Both of these qualities seem to decrease the potential usefulness for antigenic determinant prediction." From the quoted statements and the rest of the disclosure in Hopp, it is apparent that the reference was optimizing the sequence length window to optimize the value of the hydrophilicity data, and the hexameric sequences were identifying antigenic determinants having primary amino acid sequence lengths greater than 6 residues.

The Examiner's reliance on Hopp was also flawed because application of Hopp's method to the sequence of IL-22RA teaches away from the "PEDPSD" sequence of amino acids 1-6 of SEQ ID NO:3 of the pending application. Hopp expressly stated that its analytical method was "potentially very useful, even though only a single determinant can be predicted with confidence for any given molecule." Hopp, page 3827, right column, second paragraph. This limitation was explained in Hopp's admission that "the second and third highest peaks result in a mixture of correct and incorrect assignments and therefore, are less useful as predictors of antigenic determinants." *Id.* at page 3827, left column, first paragraph. Thus, only the single hexameric sequence of a protein giving the highest average hydrophilicity value according to Hopp's method will yield a useful predictor of a nearby antigenic determinant. Using the hydrophilicity values provided in Table 1 of Hopp, and performing a hexameric scan of the sequence of IL-22RA as provided in SEQ ID NO:3 of the application, one is led to an identification of amino acids 165-170, inclusive, as the single hexameric sequence of highest average hydrophilicity value in IL-22RA. That hexameric sequence is "KQREYE," which provides an average hydrophilicity value of (3+0.2+3+3-2.3+3)/6=1.65. In contrast, amino acids 1-6 of SEQ ID NO:3 of the application constitute the hexameric sequence "PEDPSD," which yields an average hydrophilicity value according to Hopp of (0+3+3+0+0.3+3)/6=1.55. Thus, the sequence from residues 165-170 has a higher average hydrophilicity value than the sequence at residues 1-6 of SEQ ID NO:3. According to Hopp, the hexameric sequence at residues 165-170 of IL-22RA may lie within, or adjacent to, an antigenic determinant, but the hexameric sequence at residues 1-6 cannot give rise to any prediction regarding an antigenic determinant. Therefore, Hopp teaches away from a hexameric antigenic peptide of IL-22RA that contains the sequence of amino acids 1-6 of SEQ ID NO:3.

Hopp was also characterized as emphasizing peptides rich in "P," "E," and "D" as recited in Hopp's Table 2. Office Action at page 3. Hopp, however, adjusted the hydrophilicity values of some amino acids, including the upward adjustment of Proline to a value of 0.0. As shown in Table 1, Hopp emphasized charged proteins such as R, D, E and K, with each of these charged amino acids receiving a hydrophilicity value of 3.0. Hopp did not disclose or suggest that the upwardly adjusted value of 0.0 for Proline elevated that amino acid into the category of significant residues contributing to high hydrophilicity values, and inspection of Table 1 in Hopp shows that Proline would be an average amino acid in terms of contribution to an average hydrophilicity value. Hopp did not teach an emphasis on peptides rich in Proline.

Based on the foregoing remarks, Applicants submit that Busfield unambiguously teaches that antigenic peptides are to be at least 8 amino acids in length, that Hopp did not disclose or suggest hexameric antigenic peptides in disclosing the analysis of hexameric sequences of a protein, and that Hopp did teach that the only hexameric sequence of IL-22RA that would be of interest as a marker of an antigenic determinant would be amino acids 165-170 of Applicants' SEQ ID NO:3, and not amino acids 1-6 of that SEQ ID NO:3. Accordingly, Busfield and Hopp, considered in combination, do not disclose each element of any one of the rejected claims and cannot provide a reasonable expectation of success in arriving at the claimed subject matter. The Examiner has not established a *prima facie* basis for rejecting any of claims 55-57 and 59 as obvious under 35 U.S.C. § 103(a) over Busfield in view of Hopp. Accordingly, the rejection has been overcome with respect to claims 55-57 (rendered moot with respect to claim 59) and the rejection should be withdrawn. Moreover, none of new claims 81-89 can properly be rejected under § 103(a) over Busfield in view of Hopp for the reasons provided herein.

B. The Rejection of Claims 58 and 60 under 35 U.S.C. § 103(a) May Properly Be Withdrawn.

The Examiner also rejected claims 58 and 60 under 35 U.S.C. § 103(a) over Busfield in view of Hopp, and in further view of Lok et al. (USPN 5,965,704; hereinafter "Lok") and Gonzalez et al. (USPN 6,133,426; hereinafter "Gonzalez"). The rejection of claim 60 has been rendered moot by cancellation of that claim. In support of the rejection of claim 58, the Examiner implicitly relied upon the characterization of Busfield and Hopp provided in rejecting claims 55-57 and 59 as obvious and in prior Office Actions. Lok was cited for the proposition that PEGylation of antigenic peptides was known in the art, but Applicants believe the Examiner was referring to Gonzalez, which was characterized in the Office Action of February 21, 2008 as disclosing humanized anti-IL 8 monoclonal antibodies and PEGylation thereof. In the Office Actions of August 18, 2006, and February 21, 2008, Lok was characterized as disclosing the elicitation of an antibody response to full-length IL-22RA. Thus, Applicants are construing the Examiner's position as relying on the characterization of Busfield and Hopp provided in support of the rejection of claims 55-57 and 59 as obvious, on Lok disclosing the elicitation of antibodies to full-length IL-22RA, and on Gonzalez disclosing humanized anti-IL 8 antibodies and PEGylation thereof.

The Examiner relied on Lok and Gonzalez for the propositions described in the preceding paragraph, and not for any proposition related to the disclosure of the IL-22RA (Zcytor11) sequence and the suggestion to use hexameric peptides thereof as antigenic peptides. Thus, the Examiner did not rely on either Lok or Gonzalez to remedy any of the deficiencies identified above with respect to the Examiner's reliance on Busfield or Hopp, and summarized below.

Busfield, in fact, does teach that the antigenic peptides must be at least 8 amino acids in length, and it is this express statement in Busfield that teaches against the use of hexapeptides, and not any disclosure in Busfield relating to preferred embodiments. Busfield expressly characterized its entire invention as involving peptides of "at least" 8 amino acids. Neither Lok nor Gonzalez can remedy this defect, and the Examiner has not asserted otherwise.

Hopp does not teach a hexameric antigenic peptide in teaching an analysis of a protein of interest by progressively scanning hexameric sequences of that protein. Rather, Hopp teaches that analysis of the hexameric sequences can lead to identification of a single hexameric sequence that is within or adjacent to the sequence of an antigenic determinant. In the specific case of IL-22RA, Hopp's method would identify amino acids 165-170 of Applicants' SEQ ID NO:3, and only that hexameric sequence, as likely being within or adjacent to the sequence of an antigenic determinant of IL-22RA. Neither Lok nor Gonzalez was cited as remedying those defects in Hopp, and neither Lok nor Gonzalez can provide such a remedy.

Based on the foregoing observations, neither Lok nor Gonzalez, considered alone or in any combination, can remedy any of the above-noted deficiencies in Busfield or Hopp. Accordingly, the Examiner has not established a *prima facie* basis for rejecting claim 58 as obvious under § 103(a) over Busfield in view of Hopp and in further view of Lok and Gonzalez. Moreover, for the reasons provided herein, none of new claims 81-89 can properly be rejected under § 103(a) over Busfield in view of Hopp and in further view of Lok and Gonzalez. Accordingly, the rejection should be withdrawn.

CONCLUSION

In view of the preceding remarks, Applicants submit that claims 55-58 and 81-89 are in condition for allowance. Expedited notification thereof is respectfully requested.

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Respectfully submitted,

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